Determinant of Drug-resistant Pulm TB

by Review Pak

Determinants of Drug-resistant Pulmonary Tuberculosis in Dr. Kariadi General Hospital, Indonesia

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Abstract— Indonesia ranked 6th from countries with the highest burden of drug-resistant pulmonary tuberculosis (PTB). A rate of 1.9% of new cases develop to be resistant and even 12% from previous treated cases. Previous studies concluded determinants of drug-resistant PTB, however, the study in Indonesia, especially in the scope of hospitals is still limited. Our study aims to explore the determinant of drug-resistant PTB in Dr. Kariadi General Hospital. We conducted a case-control study, using data from medical records. A sample of 76 cases and 76 controls have met the criterion and were involved in the study. The status of drug-resistant cases determined by rapid molecular test. We observed the subject's characteristics and determinants of drug-resistant PTB. Study shows that there is no significant difference in the subject's characteristics, i.e. age, sex, level of education, and working status between the group of cases and controls. *Chi-square* analysis shows that history of previous treatment, HIV infection, drug side-effects status, Acid-Fast Bacilli (AFB) gradation, and duration of treatment were related to drug-resistant pulmonary TB. After conducted *Binary Logistic Regression*, we concluded that history of treatment (OR=24.3; 95%CI: 8.49-69.33) and AFB gradation (OR=13.8; 95% CI: 2.76-68.60) altogether as dominant determinants of drug-resistant PTB.

Keywords—Determinant, drug-resistant, tuberculosis

I. INTRODUCTION

Drug-resistance is the most burden of the tuberculosis (TB) infection. WHO reports 153,119 drug-resistant TB cases in 2017 [1]. Many efforts have been made over the past 20 years to control TB worldwide, however, there were an estimated 9 million new incident cases of drug-resistant TB [2]. Drug-resistant TB threatening TB management and eradication programs around the world [3]. Drug-resistant TB requires extensive treatment which needs a longer duration of treatment with multiple, potentially toxic drugs and poor outcomes [4]. Approximately a number of 50% of patients with drug-resistant TB die because of it [5]. Indonesia ranked 6th from the 27 countries with the highest burden of drug-resistant TB. A number of 1.9 % new cases develop to be resistant and even 12 % in cases with previous treatment [1]. Drug-resistant TB caused by genetic mutation and the efficacy of the anti-tuberculosis drugs become ineffective. Another pivotal factor that related to drug-resistant TB is an inadequate previous treatment [6].

The previous study in Pakistan showed that drug-resistant TB is associated with previous treatment status i.e. patients with a history of previous treatment have a probability to become resistant cases 4 times compared to patients without any previous anti-tuberculosis treatment [7]. Besides the previous treatment factor, a study in Nigeria showed age and socio-economical status as risk factors of drug-resistant Pulmonary TB (PTB) [8]. Previous study in Indonesia concluded the dominant predictors of drug-resistant TB is inadequate treatment in the previous infection. Subjects with inadequate treatment have 40 times risk to get drug-resistant TB compared to subjects with adequate treatment [6].

Dr. Kariadi General Hospital is a national referral hospital in Semarang, Central Java, Indonesia that admits patient referrals from across Central Java and even nationwide. Previous studies concluded determinants of drug-resistant PTB, however, the study in Indonesia, especially in the scope of hospitals is still limited. Previous study in Dr. Kariadi General Hospital observed multi-drugs-resistant TB and concluded that duration of treatment as its predictor while the most pivotal determinant i.e. history of previous treatment was not the predictor [11]. We aimed to explore the determinant of drug-resistant PTB cases in Dr. Kariadi General Hospital.

II. METHODS

We conducted a case-control study, using the secondary data from Medical Records of PTB patients who were examined molecular rapid test in Dr. Kariadi General Hospital, Semarang, Central Java, Indonesia within last 2 years (2017 – 2019). Molecular rapid tests were conducted to determine the status of drug-resistant PTB. The study protocol was approved by the institutional ethics board committee of Public Health Department, Sports Science Faculty, Universitas Negeri Semarang (No. 052/KEPK/EC/2019).

A total of 2,345 patients recorded in the Medical Records consist of 1,267 patients with drug-resistant PTB as cases population and the rest of 1,078 patients without drug-resistant PTB as control population. A number of patients lost of follow up caused by underwent treatment elsewhere, incomplete medical records, and other reasons i.e. dropped out of the treatment or died so that finally left 410 patients with drug-resistant PTB and 268 patients without drug-resistant PTB.

Based on the minimum sample size, we determined 76 cases and 76 controls consecutively selected from the patients with the last visit recorded. (detailed subjects recruitment described in **Fig.1**)

We observed subjects characteristics, i.e. age, sex, level of education, and working status. We also observed determinants of the drug-resistant PTB i.e. history of previous treatment, HIV infection, Diabetes mellitus, drug side-effects status, Acid-Fast Bacilli (AFB) gradation, and duration of treatment from medical records provided by Dr. Kariadi General Hospital.

Data were presented in frequency and percentages based on cases and control status, since the kind of categorical data. *Chi-square* analysis was done to determine the association between determinants and drug-resistant PTB status. P<0.05 was considered statistically significant. Factors that have p value lower than 0.25 involved in the multivariate analysis. We analyzed the final model using *Binary Regression Logistic*. All analysis performed by SPSS 16.0 (IBM *Corporation*, NY, USA).
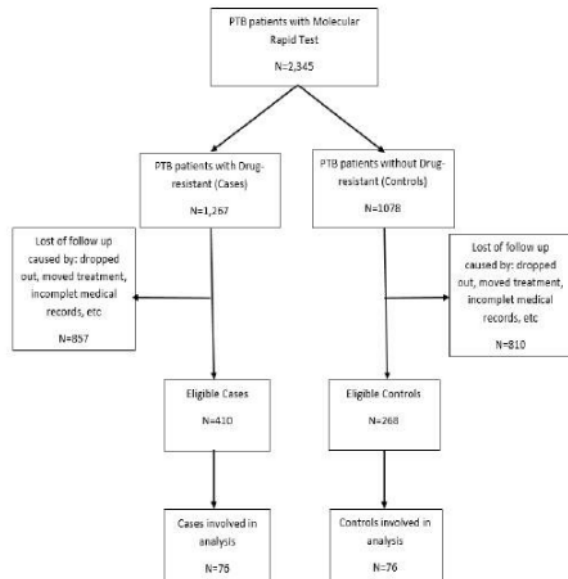

Fig. 1. Subjects selection flow chart

III. RESULTS AND DISCUSSION

Table I. showed the subject's characteristics between groups. All subjects characteristics i.e. age, sex, level of education, and working status are comparable between the cases and controls groups (p > 0.05). Descriptively, also shown that the proportion of cases tend to be higher in the younger group which is economical productive age (15-54 years old) (76.3%), a higher level of education (97.4%), and employed persons (63.2%).

Table II. showed the cross-tabulation of the determinants between groups. Almost all determinants were significantly associated with the drug-resistant PTB status, i.e. history of

previous treatment, HIV infection, drug side-effects, AFB gradation, and duration of treatment (p<0.05). History of previous treatment in cases group consist of Failed (23.7%), Dropped-out (9.2%), and Relapse (38.2%). AFB gradation significantly compared in the positive and negative category. In positive AFB, 'Scanty' group proportion higher (59.2%) than others i.e. 1+ (23.7%), 2+ (13.2%), and 3+ (0%). Duration of treatment showed significantly different in the cutt-off 6 month category.

TABLE I. Subject's Characteristics

Characteristics	Drug-resistant PTB		*P* value*
	Yes	No	
Age (years old)			0.112
15 – 54 (n;%)	58; 76.3	48; 63.2	
≥ 54 (n;%)	18; 23.7	28; 36.8	
Sex			0.330
Male (n;%)	34; 44.7	41; 53.9	
Female (n;%)	42; 55.3	35; 46.1	
Level of education			
High school or lower (n;%)	74; 97.4	72; 94.7	0.677
College or higher (n;%)	2; 2.6	4; 5.3	
Working status			
Employed (n;%)	48; 63.2	41; 53.9	0.323
Unemployed (n;%)	28; 36.8	35; 46.1	

*Chi-square test

Binary logistic regression concluded that the history of previous treatment (OR=24.3 95% CI: 8.49-69.33) and AFB gradation (OR=13.8 95% CI: 2.76-68.60) altogether were the most pivotal determinants of drug-resistant PTB with the total contibution of 57,5% and the rest 42.5% influenced by other factors as shown in **Table 3 and Fig 2.**

Current study showed the most dominant determinants of drug-resistant PTB were the history of previous treatment and AFB gradation. These findings consistent and similarly with previous studies [11-14], while the recent study in Dr. Kariadi General Hospital showed that previous treatment was not the determinant of drug-resistant PTB [9]. The current study confirmed well-known common knowledge of the determinants for drug-resistant PTB. History of previous treatment contributed by failed, dropped-out, and relapse cases.

Failed cases can be caused by inadequate treatment, non-compliance patients /fail to take TB drugs continuously, sputum smear-positive at two months of treatment, the existence of comorbidity, and use of traditional medicines or herbs. [17] Factors that associated with dropped-out TB management cases were HIV positivity, alcoholism, low education level, other co-morbidities, younger patients, and no DOTS management [17]. Relapse cases could be caused by the severity of TB infection signed by the existence of cavitation and positive culture at 2 months [20-21], HIV infection, non-compliance, age, and substance use [20-22] Although more detailed actually can be clearly explained, however, since the current study used secondary data, limited information restricts comprehensive explanation.

TABLE II. Determinants of Drug-resistant Tuberculosis

Determinants	Drug-resistant PTB		P value*	OR (95 % CI)
	Yes	No		
History of previous treatment				
Cases with previous treatment (n;%)	**54; 71.1**	**8; 10.5**	**0.000**	**20.9 (8.61 – 50.53)**
- Failed (n;%)	18; 23.7	0; 0		
- Dropped-out (n;%)	7; 9.2	1;0.33		
- Relapse (n;%)	29; 38.2	7; 9.2		
New cases (n;%)	**22; 28.9**	**68; 89.5**		
Hostory of Diabetes Mellitus				1.130 (0.570-2.240)
Yes (n;%)	25; 32.9	23; 30.3	0.861	
No (n;%)	51; 67.1	53; 69.7		
HIV infection				0.05 (0.007-0.422)
Yes (n;%)	1; 1.3	15; 19.7	0.001	
No (n;%)	75; 98.7	61;80.3%		
Drug side-effects				15.426 (6.461-36.830)
Yes (n;%)	49;64.5	8; 10.5	0.000	
No (n;%)	27; 35.5	68; 89.5		
AFB gradation				
Positive (n;%)	**73; 96.1**	**49; 64.5**		**13.4 (3.86-46.64)**
- 3+ (n;%)	0; 0	9; 11.8		
- 2+ (n;%)	10; 13.2	24; 31.6	**0.000**	
- 1+ (n;%)	18; 23.7	5; 6.6		
- Scanty (n;%)	45; 59.2	12; 15.8		
Negative (n;%)	**3; 3.9**	**26; 34.2**		
Duration of treatment (months)				
>6 (n;%)	**12; 15.8**	**2; 2.6**		**6.9 (1.50-32.16)**
≤6 (n;%)	**64; 84.2**	**74; 97.4**	**0.005**	
- 3-6 (n;%)	31; 40.8	5; 6.6		
- 1-2 (n;%)	8; 10.5	1; 1.3		
- <1 (n;%)	25; 32.9	68; 89.5		

*Chi-square test

AFB: Acid-Fast Bacilli

TABLE III. Binary Logistic Regression

Determinants	B	Adjusted OR (95% CI)	p value*
History of previous treatment	3.19	24.3 (8.49-69.33)	0.000
HIV infection	-1.97	1.4 (0.10-1.98)	0.145
AFB gradation	2.62	13.8 (2.76-68.60)	0.001
Constant	-3.30	0.037	0.000

*Binary Logistic Regression test

$R^2=0,575$ (*Nagelkerke*)

This study also found that AFB gradation was related to the drug-resistant PTB. The higher gradation of AFB the higher risk to get drug-resistant TB [16], however, in this study the trend did not show the relationship, it might be a limited amount of subjects in this study, even the number of '3+ AFB' patient was 0 in the case group. Previous study concluded that positive AFB had risk of 6.54 times to get drug-resistant TB [16].

Although the most dominant determinants were the history of previous treatment and AFB gradation, however, in the *Chi-square* analysis, besides the dominant determinants, we also concluded that HIV infection, drug side-effects, and duration of treatment as other determinants of drug-resistant PTB. These findings also in accordance with other studies [12-15].

HIV infection was associated with drug-resistant PTB. The previous study concluded that HIV positivity is related to MDR-TB. [11,16]. The current study showed 49 cases with the existence of drug side-effects i.e. nausea, vomitus, tinnitus, and arthralgia. Subjects with a history of drug side-effects existence tend to be drug-resistant PTB case. It can be explained that after the existence of side-effects caused discontinuing the treatment without consultation to the health provider. This finding accordance with the previous study that concluded the existence of drug side-effects had 3.08 times to be drug-resistant TB [6].

Duration of treatment was also related to drug-resistant PTB based on bivariate analysis. This finding also have been proved by previous study in Dr. Kariadi General Hospital as the most dominat factor that related to the MDR-TB cases. Patients with duration of treatment more than 7 months had 3.23 times higher risk to be resistant [9]. Based on bivariate analysis, current study also concluded that patients with duration of treatment more than 6 months would have 6.9 times higher risk to get drug-resistant PTB case as shown in **Table II.**
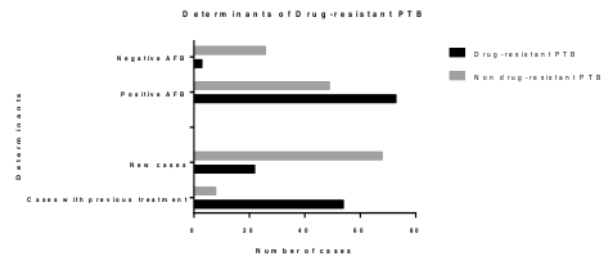

Fig. 2. Determinants of drug-resistant PTB

The case proportion in the descriptive data presentation also showed tend to be higher in younger age (15-54 years old). Previous study even concluded that age category which is productive economically (30-59 years old) significantly tend to be the case of drug-resistant TB [10-11].

IV. CONCLUSION

The current study concluded in this study population that most dominant determinants of drug-resistant PTB were the history of previous treatment and AFB gradation. Altogether the history of previous treatment and AFB gradation were associated with drug-resistant PTB with the contribution of 57.5 %. Future study that involved more comprehensive determinants not only using secondary data from medical records, but captures primary data i.e. more detailed severity and type of the mycobacterium, more detailed person, place, and time in previous treatment history, drug side-effects,

duration of treatment, and other parameters should be conducted to elucidate the determinants more clearly.

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FINAL GRADE

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GENERAL COMMENTS

Instructor

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